Reprinted from the BRITISH MEDICAL JOURNAL, *December 13th, 1924.*

IMMUNITY, WITH SPECIAL REFERENCE TO SPECIFICITY AND THE INFLUENCE OF NON-SPECIFIC FACTORS.*

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IF I can contribute anything of interest to the discussion to-day it will be based upon work which has been carried out during the past twenty-five years in a large laboratory where, in addition to a considerable amount of research work, probably 100,000 closely controlled experiments have been done in connexion with the production and testing of serums, vaccines, tuberculins, and laboratory reagents. For the purpose of this paper my colleagues have generously placed at my disposal the whole of their work, both published and unpublished.

When carrying out the large number of tests mentioned the various laboratory workers have been constantly on the watch for the appearance of any factors that might affect the accuracy of the test or produce unexpected results. Apart from one exception, referred to later, we have never had any evidence that any "non-specific" factor—in the sense in which this word is ordinarily used—has affected our results. My apology for emphasizing these laboratory experiences is that they must influence my point of view; in this discussion I can represent mainly and almost solely the point of view of the laboratory worker.

When faced with a new method which appears to promise prevention or cure, the strong tendency of the laboratory worker is to say in effect, "By a certain injection or treatment I can produce in every animal certain accurately measurable symptoms or lesions, or, it may be, death. Will this new method prevent these lesions or cure the animal in an experiment repeated one hundred times?" This point of view has been present throughout my consideration of the whole problem.

It is expedient to try to define the subject we are considering. It seems to be impossible to define "specificity" concisely, because the word has been used in therapeutics

* A paper read in opening a discussion in the Section of Pathology and Bacteriology at the Annual Meeting of the British Medical Association, Bradford, 1924.

in several senses. In the immunological field the word " specificity " indicates adjustment of the remedy to the infecting agent, even to the particular strain of organism. " Specificity " has also been used as between the infecting organism and the host. We all agree that diphtheria antitoxin is a " specific " remedy for diphtheria in the original immunological sense, and that quinine is a " specific " for malaria in the second sense in which the word is used. We are also all agreed in considering the use of *coli* vaccine for the treatment of typhoid fever, or the injection of milk or peptone into sufferers from asthma or arthritis, as instances of " non-specific " treatment.

Now the whole of the tests to which I referred above have been based upon the original rigid doctrine of specificity. We know that diphtheria antitoxin will save the life of a guinea-pig injected with an otherwise fatal dose of diphtheria toxin. We believe this protection occurs through a definite chemical or physico-chemical reaction between the toxin and the antitoxin. We know of no other substance which is neutralized by diphtheria antitoxin. We know of no other substance which will neutralize the action of diphtheria toxin and that alone. We believe also that antitoxin cannot be produced except as a result of the action on the living animal of a small dose of toxin. We believe that we can detect 0.00000025 c.cm. of a " high potency " diphtheria antitoxin by the intradermal method. If a minute quantity of diphtheria toxin is injected into a guinea-pig's skin it will produce within twenty-four hours a red flush with slight thickening of the skin, but if a minute amount of antitoxic serum be added to the toxin before injection the toxin will be neutralized and the flush will not appear. Similarly we believe that " tuberculin " injected into a tuberculous guinea-pig will produce a striking fall of temperature and death, the autopsy showing characteristic engorgement of the tuberculous tissue nearest the injection, engorgement of spleen and liver and of all tuberculous foci in the body. I know of nothing that will produce this picture but " tuberculin "—that is, some product of the tubercle bacillus.

It may be of interest to recall the problem set the laboratory early in the war, when tetanus and gas gangrene appeared in wounded men. It was easy to produce antitetanus serum which would protect an animal against the attack of tetanus otherwise inevitable after the injection of ordinary soil containing tetanus spores. It was soon discovered that *B. welchii* was the cause of much gas gangrene, and a serum was produced, but it was found in the laboratory that if one obtained material from cases of gas gangrene and injected it into animals protected with antitetanus serum and anti-*welchii* serum, an occasional sample produced gas gangrene in the protected animals. Further research showed that the organism responsible was the *Vibrion septique*. The problem of making anti-*Vibrion septique* serum was attacked and solved. But still it

happened from time to time that an animal injected with material from some case of gas gangrene died of gas gangrene, even though protected with antitetanus, anti-*welchii*, and anti-*Vibrion septique* serum; from these animals another organism, *B. oedematiens*, was obtained and an antiserum prepared. In 1918 it was possible to provide in the laboratory a serum a few cubic centimetres of which would protect an animal injected with mixed cultures of *B. tetani*, *B. welchii*, *Vibrion septique*, and *B. oedematiens*. The whole of this work in several allied laboratories was based on the rigid laws of specificity.

I may recall another interesting instance of specificity. We repeatedly make a serum 1 c.cm. of which will protect a mouse against 50 million fatal doses of living pneumococcus Type I; yet we find that this serum will not protect a mouse injected with a small quantity of Type II pneumococcus, which is indistinguishable by morphological or biochemical reactions from Type I pneumococcus. There are at least two, probably three, groups of *B. botulinus* indistinguishable except by agglutination test and by the capacity to produce serum protective only against the homologous bacillus or toxin. Apparently there are two types of the virus of foot-and-mouth disease, for immunization with one will apparently protect against the first strain only and not the second. The foregoing are instances of rigid specificity in connexion with infectious or bacterial disease.

Up to the present we have been considering only phenomena based on rigid specificity. It was long before the laboratory worker found any phenomena reproducible with certainty and accurately measurable in which these rigid laws of specificity appeared to need some relaxation or redrafting. There are a series of such phenomena. One of the most familiar is the Wassermann reaction; the serum of the syphilitic patient reacts with an antigen made from the heart muscle of a healthy human being or an animal that has not been in contact with syphilis. It is of interest that in the earliest application of this test to the diagnosis of syphilis it was considered necessary to use a specific extract of the liver of a syphilitic foetus. When a patient suffers from typhus fever, agglutinins of the X 19 bacillus appear, though there is no certain causal relationship between this bacillus and the disease. In the Forssman phenomenon we find that an injection of guinea-pig kidney tissue into a rabbit causes the appearance of antibodies which will lyse sheep red blood cells. We may explain this by assuming that an essential antigen to sheep red cells happens also to be present in kidney of guinea-pig, horse, etc., but *not* in guinea-pig red cells, etc.

While no substance other than specific antibody may neutralize a toxin, or any other substance than toxin cause production of antitoxin, the *availability* for neutralizing action, of antibody already formed, may be influenced in

several ways. It was long ago shown that an animal whose blood over a long period contained a certain stable concentration of tetanus antitoxin may lose in repeated bleedings as much antitoxin as was contained in the total blood at the commencement of the experiment, and yet, without further injection of tetanus toxin, it may, after the bleeding, replace in the circulation as much antibody as was abstracted. Glenny and Sudmersen[1] showed that a guinea-pig immunized with diphtheria toxin maintained the same concentration of antitoxin in its blood for a period of from one to two years; during this time it almost doubled its

TABLE I.—*Actively Immune Rabbits injected with Peptone.*

Rabbit.	Previous Injection.	Weight in Grams.	Peptone Injected.	Antitoxic Value.	
				Before.	24 hours after Peptone.
G.11	12 months	3875	9.8 c.c. 10% Witte	1/20	1/25
G.12	16 ,,	2725	0.68 c.c. 10% Witte	1/40	1/40
G.13	15 ,,	2950	9.8 c.c. 10% Armour	1/2000	1/2000
G.17	15 ,,	3425	1.15 c.c. 10% Armour	1/5	1/5

TABLE II.—*Effect of Peptone on Secondary Stimulus Response.*

(Actively immune rabbits injected with 5 c.c. B.1092 (toxoid) 24 hours after peptone.)

Rabbit.	Previous Injection.	Weight in Grams.	Peptone Injected.	Antitoxic Value.	
				Before.	7 days after Secondary Stimulus.
					units per c.c.
G.22	16 months	2700	0.9 c.c. 10% Armour	1/250	4
G.23	16 ,,	2750	—	1/50	12
G.211	3 weeks	1900	0.45 c.c. 10% Witte	1/250	4/5
G.213	3 ,,	2100	—	1/100	1/5
G.212	3 ,,	2100	—	1/5	12
G.214	3 ,,	3175	0.13 c.c. 10% Witte	1/5	3

weight and gave birth to eight young, the blood of which contained at birth the same concentration of antitoxin as that of the mother throughout the observation. It is fairly certain that this guinea-pig had produced during the experiment and without any further stimulus by toxin injection at least as much antitoxin as its blood contained at the beginning of the experiment. I have shown that from a horse whose serum is lytic for sheep red cells one can withdraw in repeated bleedings as much haemolysin as was present initially, and yet the animal without the injection

of further sheep red cells will replace in the circulation—conceivably from stores in the tissue, but almost certainly by fresh production—the whole of the haemolysin abstracted. It is conceivable that other stimuli than the abstraction of blood might raise the titre of antibodies in the circulating blood, and attempts have been made to increase the production of antitoxin such as diphtheria antitoxin by the injection of agents other than diphtheria toxin. It was thought some years ago that the injection of pilocarpine

TABLE III.—*Effect of Intravenous Injections of Peptone on the Immunity Produced by the Injection of Diphtheria "Toxoid."*

			Number of Guinea-pigs showing an Immunity Index of—		
			12 days.	14 days.	Over 14 days.
Controls 5 c.c. B.1092 (toxoid)			0	1	2
			0	2	4
			0	2	4
			0	1	1
			0	6	11
Peptone Injected.	Dose in mg. per gram of body weight.				
Witte.	1/2 or less ...	Before toxoid	0	2	6
	1/4	11 and 13 days after	0	2	4
	1/8	11 and 13 days after	0	2	1
	1/8	11 and 13 days after	1	3	2
	less	11 and 13 days after	—	2	4
			1	11	17
Armour.	1/6	Before toxoid	0	2	1
	less	Before toxoid	0	3	3
	1/6	3 and 5 days after	0	1	2
			0	6	6
	1/3	3 and 5 days after	0	2	1
	1/3	3 and 7 days after	2	0	0
	1/6	6 days after	1	3	2
	1/6	8 days after	2	1	1
	1/6	11 and 13 days after	1	2	0
	1/6	11 and 13 days after	0	4	2
	less	11 and 13 days after	1	3	2
			7	15	8

would increase the yield of antitoxin from a stud of horses, but this method has not justified the original claims made. Recently Copenhagen workers have stated that the use of injections of manganous chloride has increased the yield of diphtheria antitoxin from horses. In our hands and in those of some other investigators this method has not increased the yield of antitoxin. The statement has also been made that injections of other non-specific agents—peptone, etc.—will raise the titre of antitoxin in the blood.

My colleague, Mr. Glenny, injected peptone into a series of rabbits some of which had been immunized a year or more previously and still had a small amount of antitoxin in the body or circulation. In none of these rabbits was the antitoxin concentration of the blood affected by the injection of peptone. Half of a further series of rabbits which had a basal immunity received a second injection of diphtheria toxoid—that is, a secondary stimulus—and half received the injection of diphtheria toxoid twenty-four hours after an injection of peptone. The injection of the peptone does not seem in any way to have affected the result.

Yet Dale and Kellaway with Cowell found that "non-specific" substances such as peptone or normal horse serum had an interesting effect on sensitized animals. These workers showed that if one injected serum protein or crystalline egg albumen into a series of guinea-pigs the animals became sensitized by the albumen, so that the well known phenomena of fatal anaphylaxis immediately followed the intravenous injection of small doses of protein; but if to a sensitized guinea-pig an injection of normal horse serum or peptone was given prior to the injection of the sensitizing protein the animal was able to tolerate the dose of albumen that killed his fellow.

Kellaway and Cowell examined and rejected the suggestion that the antibody to the egg albumen, present in the sensitized guinea-pig, is released by the action of the injected peptone from its home in the body cells and appears free in the circulation, ready there to meet and neutralize the incoming albumen. They concluded that the "desensitization" of the sensitive animal was due to some temporary alteration of the molecular constitution and reactivity of the muscle cells of the body. It may be that this experiment is one of a series of phenomena that have some general resemblance to each other. We may imagine that one can distract the attention of the antibody-manufacturing apparatus of the body so that it does not function as it would were its attention not otherwise engaged; one may, so to speak, "crowd out" a certain function of the apparatus. My colleague, Mr. Glenny, finds a suggestion of this phenomenon in several series of experiments on immunity in connexion with diphtheria toxin. If one injects a mixture of diphtheria toxin and antitoxin into a rabbit the animal will quickly become immune. If, however, one gives an injection of cow serum to a rabbit and after an interval of four weeks gives another injection of cow serum, followed four days later, when the formation of precipitin in response to the second injection of cow serum is in full flood, by an injection of a mixture of diphtheria toxin and horse diphtheria antitoxin, the prophylactic mixture now entirely fails to immunize the animal. Apparently the serum factory in the rabbit's body is so fully engaged that it has no energy to spare to make diphtheria antitoxin in response to the injection of prophylactic.

We now arrive at the more definite consideration of measures commonly considered as "non-specific." We may here put a series of questions.

1. Do non-specific agents release protective antibodies into the circulation? I can find no clear proof based on animal experiment that they do. But one series of experiments bearing on this point may be of interest. Mr. Glenny has very kindly allowed me to quote from an unpublished paper a curious result he has obtained. If one injects diphtheria prophylactic—either a mixture of toxin and antitoxin similar to the prophylactic used in immunizing human patients against diphtheria, or a diphtheria toxoid—into a guinea-pig, the animal does not show any immunity for some little time; the length of time depends on the efficiency of the prophylactic. After a period of a few weeks the injected animal is "Schick tested" each week. At first the result of the test is positive, but after a varying number of weeks the weekly test gives a negative result. The number of weeks elapsing before this negative result is obtained is called the immunity index. A low index obviously denotes a good antigen, a high index a poor antigen. From Table III we see that diphtheria toxoid in an untreated animal gives on the average an index of 14 or higher, and animals treated with Witte peptone or small doses of Armour peptone give an index of 14 or higher; but the interesting result is that guinea-pigs receiving fairly large doses of Armour peptone gave in twenty-two instances out of thirty an index of 14 or less. It would take a great deal of work and a long series of control experiments to make certain that this result is "significant" in the statistical sense, but one cannot resist the conclusion that the lowering of the index—that is, the increase in the efficiency of the immunization—is a direct result of the injection of the peptone.

2. Do these measures act favourably on specific infection? Through the kindness of Dr. Auld and Dr. Gow we have had the opportunity of testing on animals the effect of injections of stocks of Witte and Armour peptone which had given favourable results in the treatment of human beings. These peptones were used in the laboratory in various experiments. I am indebted to three of my colleagues for some attempts to discover whether injections of these peptones could produce any effect in animals injected, together with adequate controls, with a known minimal lethal dose of various agents. I chose a typical toxin—diphtheria: the pneumococcus—cause of a typical bacterial infection; and a bacillus that acts probably partly by intoxication and partly as a bacterial infection—*B. dysenteriae* Shiga. These three agents were chosen because we are constantly experimenting with them and the exact doses of the various agents and the reactions of the animals thereto were well known to us; we could thus feel fairly confident that no obvious fallacy in the experiments would be overlooked.

Diphtheria Toxin.—A matured toxin was taken, the minimum lethal dose of which was known. Four guinea-pigs were given one certain fatal dose; all were dead by the fifth day. Four others were given Armour peptone (1/6 mg. per gram of body weight intravenously) twenty-four hours previously; all four were dead by the fifth day. The peptone had no influence on the time of death.

Culture of Pneumococcus.—Two series of experiments were carried out in which 98 mice were used. A dose of culture (0.0000001 c.cm.) was given to the whole of the first series of mice. The peptones (Armour and Witte) were given intravenously twenty-four hours after the pneumococcus culture. Of the 10 mice receiving the culture alone, 7 died; of 32 receiving the peptones after the culture, 18 died. In a second series a more virulent culture was used. Of 12 mice injected with culture 11 died; of 35 mice receiving culture followed by peptones 30 died. No significant difference between the death rate of those receiving culture alone and those receiving also Armour and Witte peptone is discernible. Three doses were chosen. The smallest corresponds fairly closely per gram of body weight with that ordinarily injected by clinicians into human beings; the largest, or " shock " dose, is near that which produces a definite temperature disturbance and obviously affects the behaviour of an animal, and is not far below the lethal dose; a dose halfway between these was also used. The figures of the two experiments do not show any influence, either favourable or unfavourable, exercised by the peptone.

Dysentery (Shiga) Toxin.—Two doses of toxin were chosen. In the first series 0.1 mg. of toxin, in the second 0.15 mg. was mixed with a standard quantity of antitoxin—that is, 0.025 c.cm. It was known that the lower dose of toxin in the toxin-antitoxin mixture would kill about 50 per cent. of mice; it killed in this experiment 3 out of 6 injected. The larger dose of toxin killed all of 6 mice injected. The toxin-antitoxin mixtures were given to two series of mice, groups of which received the three chosen doses of peptone six hours later. In the first series, of 18 mice injected 9 died; in the second, of 23 mice injected 21 died. The peptone appears to have had no influence on the results.

The net result of these experiments is that when we used animals receiving these particular doses at the times indicated, no protective or curative effect could be traced in any of these intoxications or infections. It is, of course, possible that with other doses and other time relationships different effects might have been obtained. It is also true that these infections and intoxications constituted a severe test and are not those in the treatment of which the clinician has obtained his most favourable results. We cannot easily produce in animals either chronic arthritis or conditions such as asthma, hay fever, etc., and it is in diseases of this kind that careful clinicians have convinced themselves that favourable results follow the use of these peptones. Statements are also made that the administration of non-specific agents may protect animals against various alkaloids. We have examined only one of these statements. Starkenstein[2] stated that milk would protect rabbits against a fatal dose of strychnine given about an hour later. My colleague, Dr. Trevan, took two series of rabbits, six in each. The rabbits were divided into pairs of approximately equal weights; to one rabbit of each pair was given 0.2 mg. of strychnine intravenously per kilo of body weight; to the other, 5 c.cm. of milk per kilo were given intravenously between half and one hour before the dose of strychnine.

Of the six receiving strychnine and no milk, four died; of the six rabbits receiving milk and strychnine, three died. The administration of the milk has apparently not influenced the result of the injection of strychnine.

3. Are non-specific measures "activating agents"? If we knew more exactly how the various infections and intoxications produced their results it would help us in our consideration of the clinical records of "successful" cases of protein therapy. To take a crude illustration: if we knew that a given toxin—for example, that causing asthma—produced its symptoms by stimulation of the vagus nerve and that a certain alkaloid *x* could correspondingly depress the activity of that nerve, we could conceive that the alkaloid *x* or a peptone containing it might cure asthma. Dale and Miss Robertson have shown that the toxin of *Vibrion septique* has a digitalis-like action and produces a great fall of blood pressure, and that antitoxin. whether given previously to the animal or mixed with the toxin before injection, prevents this fall of blood pressure.

But, unfortunately, we have very little accurate knowledge on which to base hypothesis. If we knew that the occurrence of a leucocytosis would favour cure in pneumonia, we could readily see that the injection of substances of the nuclein and the tallianine class, which cause a leucocytosis as well as an increase in opsonins, might act advantageously in the treatment of pneumonia. Unfortunately we have no certain evidence that the injection of such substances will protect or cure either experimental animals or human beings suffering from pneumonia.

We know that the injection of various non-specific agents may produce great changes in the blood, and changes in coagulability, in the proteins, cellular elements, and platelets. It is easily conceivable that these changes are associated with changes in some natural mechanism of defence, differing from those ordinarily recognized by immunologists.

It is tempting to entertain the suggestion that any injury to body cells, however caused, calls into play the appropriate defensive mechanism and that whether this injury to cells be caused by the injection of casein, vaccine, or peptone, or, as in the recent deeply suggestive results of Wright and his colleagues, by the reinjection of treated blood or by exposure to light stimuli, the effect is a stimulation of natural defence in which presumably the leucocytes play an important part. Defensive processes other than those ordinarily recognized by immunologists have been outlined by Dale in his suggestive discourse at the Royal Institution in May, 1922. (See also *Physiological Reviews*, iii, 3, 1923.) In considering the conception of chemotherapy brought forward by Ehrlich, and his own researches with derivatives of emetine, Dale draws attention to the evidence indicating that Ehrlich's original hypothesis of the direct parasitotropism of the "chemo-

therapeutical" group of drugs does not fully explain the phenomena observed. He points out that the action of emetine compounds in the treatment of dysentery, of salts of antimony in kala-azar and bilharziasis, and of "205" and salvarsan in spirochaetal and trypanosome infections, cannot be fully explained by the effects of these drugs on the various infecting agents in the test tube. The body cells must presumably play an intermediate and all-important part in producing the favourable therapeutic effect of these drugs; possibly a new therapeutic agent is formed by the union of the drug and the patient's cells, or a specific product formed by the body cells in response to the injection of the chemotherapeutic agent.

This mode of action we are considering is presumably essentially different from the direct physical or physio-chemical union between a toxin and its antitoxin. It is possible that the injection of non-specific protein "activates" groups of defensive body cells in a manner similar to that hypothecated for the chemotherapeutic agents above mentioned.

4. Is the evidence that the non-specific agents have any favourable remedial effect clear and indisputable? Before reviewing the difficulties the clinician must face in endeavouring to prove any hypothesis it may be of advantage to pause for a moment and consider the nature of the proof demanded in an immunological laboratory. The determining of a minimum lethal dose or the test dose of a toxin or antitoxin will serve.

Tables IV and V show the results obtained in endeavouring to determine the lethal dose and test dose of dysentery (Shiga) toxin. Whereas we must use 0.04 mg. of toxin for 20 gram mice in order to cause 100 per cent. of deaths, it is not until we drop the dose to 0.005 mg. that we find that 75 per cent. of the mice survive. When titrating the toxin against a fixed dose of antitoxin we find that it is necessary to take 0.2 mg. of toxin before we get 100 per cent. mortality, whereas 0.05 mg. kills from 25 to 30 per cent. of animals.

Dr. Trevan has kindly allowed me to quote, from a paper he is preparing, some results of injecting insulin into mice: whereas a dose of 0.0006 mg. per 20 gram mouse may produce hypoglycaemic convulsions or death in an occasional animal (4.5 per cent.), a dose one and a half times as large will cause convulsions or death in 45 per cent., and it is not until we give a dose four times as great that we obtain convulsions or death in almost every mouse injected. If the range be thus wide when we use inanimate toxic agents, it will be much wider when using living culture for our test; in properly controlled experiments, in order to kill 100 per cent. of animals we may, then, require ten or more times as much as will kill an occasional animal. Therefore if the statement that a certain "non-specific" medicament will protect against a

lethal dose of culture were made we should demand a very large number of control animals before we should be ready to accept the statement.

We realize from these figures that even where we have complete control of the animals under treatment we must proceed statistically, and, in order to prove indubitable protection or cure, must use a considerable number of experimental and control animals. In transferring his attention from laboratory experiments to results obtained at the

TABLE IV.—*Minimum Lethal Dose ; Shiga Toxin AA.*
(Intravenous Injection : Mice.)

Amount of Toxin in mg.	No. Dying.	No. Living.	Per-centage Deaths.	Amount of Toxin in mg.	No. Dying.	No. Living.	Per-centage Deaths.
0.1	1	0	100	0.015	8	6	57
0.05	1	0	100	0.01	9	9	50
0.04	6	0	100	0.0075	5	7	42
0.03	5	1	83	0.005	4	12	25
0.025	13	3	81	0.0025	0	8	0
0.02	13	3	81				

TABLE V.—*Determination of "Test Dose" of Toxin AA.*
(Intravenous Injection : Mice. Antitoxin C.950, 0.025 c.c. constant.)

Amount of Toxin in mg.	No. Dying.		No. Living.		Percentage Deaths Seventh Day.		Per-centage Deaths Fourth Day.
	R.	S.	R.	S.	R.	S.	R.
0.25	22	—	0	—	100	—	100
0.2	35	14	0	0	100	100	88
0.15	32	21	3	1	93	95	68
0.125	15	16	5	2	75	84	55
0.1	11	8	9	11	54	44	20
0.05	3	3	5	10	37	23	37

R. and S. were two observers working independently in separate laboratories.

bedside, the laboratory worker becomes vividly alive to the fact that the difficulty of proof where human beings are concerned is incomparably greater than in laboratory experiments, and that the clinician has a more difficult task than his colleague who works with animals and test tubes. The laboratory worker must pay a profound tribute of respect to the achievements of the clinician in the face of immense difficulties. But this sympathy and admiration must not allow us to lower the standard of evidence that

we ask before we are convinced. We remember that the guinea-pig is insusceptible to suggestion, and that it does not know whether it is to expect amelioration or not from the material given. Some of the evidence brought forward in support of non-specific therapy will not bear any reasonable critical examination, and is presumably born of the courageous optimism of the clinician in his deep wish to benefit the sick. It is particularly in the treatment of the infections that the evidence appears to me to fail under criticism. It may be that the administration of *coli* vaccine does materially influence the course of typhoid fever and of arthritis, but we feel that we must have more evidence before accepting the claim. Remembering the effect of non-specific proteins in anaphylaxis shown by Dale and his co-workers, one is more prepared to believe that non-specific agents may have some effect in the group of diseases consisting of asthma, hay fever, the specific urticarias, and migraine. After seeing the results of cases which Dr. Auld very kindly showed me, it is difficult not to believe that the peptone injections have been the cause of the large measure of relief following on courses of injections given to patients who had suffered from persistent asthma for many years.

In reviewing the whole question we may ask ourselves, What will the future history of protein therapy be? Are current views of the real usefulness of protein therapy so firmly based that the treatment will become a permanent addition of value to our therapeutic armoury? We remember that non-specific therapy has been advocated for about two decades, and that its use is still limited to a comparatively small number of medical practitioners; one does not find in the records of the past few years any clear evidence that the mortality of typhoid fever or the severity of the attack is always favourably influenced by the use of non-specific vaccines, or that non-specific agents have been so successful in the treatment of chronic arthritis and similar diseases that we can hold out great hope of cure or material alleviation to every sufferer from this disease.

The laboratory worker must pause in self-examination and wonder whether such thoughts arise from deep-rooted orthodox conservatism and a repugnance to the acceptance of anything new; but he will feel justified in clearing himself, at least to some extent, when he remembers how avid the whole medical world is for new things of proved value in the fight against disease, the eagerness with which it has seized pituitary extract, adrenaline, salvarsan, "205," and insulin. A doubt must perforce make itself felt in our minds when we compare the slowness of the acceptance of the claims made for non-specific therapy.

In conclusion, the laboratory worker must always remember that, while his object is to seek truth, the physician has the harder task—he must also cure his patient. When we attempt to form an opinion as to the

exact degree of permanence and truth there is in the present clinical estimate of the utility of non-specific agents, we must retain an open mind and be prepared to believe in convincing evidence when it is produced, however little it may accord with the immunological explanations hitherto current in the laboratory. After all, it is difficult to conceive of a more rigid specific requirement than that the ovum of a given species will not develop unless fertilized by the specific sperm of that species, and yet Loeb's " fatherless frog " must again warn us that nothing is incredible except that which has not yet been proved.

References.

[1] *Journ. of Hygiene*, 1921, xx, 191. [2] *Muench. med. Woch.*, 1919, vol. 66, 1.